IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

OSI PHARMACEUTICALS, LLC and GENENTECH, INC.,	)	
Plaintiffs,	)	
v.	)	C.A. No. 15-772 (CFC) (SRF) CONSOLIDATED
APOTEX INC. and APOTEX CORP.,	)	
Defendants.	)	

STIPULATED FINAL JUDGMENT

WHEREAS, Plaintiff OSI Pharmaceuticals, LLC ("OSI") holds an approved New Drug Application ("NDA") under Section 505 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 355, for erlotinib hydrochloride tablets (NDA No. 021743), which it sells under the trade name Tarceva®;

WHEREAS, Plaintiff OSI is the owner of U.S. Patent No. 6,900,221 (the "'221 patent") and Plaintiff Genentech, Inc. ("Genentech") is an exclusive licensee of the '221 patent;

WHEREAS, the use of Tarceva is covered by one or more claims of the '221 patent, which have been listed in connection with Tarceva in the FDA's publication, Approved Drug Products with Therapeutic Equivalence Evaluations, referred to as the "Orange Book;"

WHEREAS, Defendant Apotex Corp. filed Abbreviated New Drug Application No. 208396 (the "ANDA") for approval to manufacture and sell a generic version of Tarceva prior to the expiration of the '221 patent;

WHEREAS, Defendant Apotex Corp. is the U.S. agent for Defendant Apotex Inc. for ANDA No. 208396 (Apotex Corp. and Apotex Inc. together, "Defendants");

WHEREAS, Plaintiffs OSI and Genentech (together, "Plaintiffs") asserted claims 44, 46, 47, and 53 of the '221 patent against Defendants in this Action;

WHEREAS, on January 9, 2017, the Patent Trial and Appeal Board ("PTAB") instituted an *Inter Partes* Review, Case No. IPR2016-01284, concerning certain claims of the '221 patent (the "IPR Proceeding");

WHEREAS, on January 25, 2017, at the parties' joint request, the Court stayed this Action pending the PTAB's decision in the IPR Proceeding, including any appeal to the United States Court of Appeals for the Federal Circuit ("Federal Circuit") (D.I. 74, hereinafter the "January 25, 2017 Order");

WHEREAS, Plaintiffs agreed to not assert claim 47 of the '221 patent (D.I. 74);

WHEREAS, according to the terms of the January 25, 2017 Order, Defendants' ANDA and the product described therein (the "Apotex ANDA Product") infringe claims 44, 46, and 53 of the '221 patent and do not infringe claims 1-43, 45, 47-52, and 54-79 of the '221 patent;

WHEREAS, Plaintiffs and Defendants agreed that the outcome of any validity and/or enforceability arguments in this Action would be governed by the decision of the PTAB in the IPR Proceeding, including any appeal to the Federal Circuit and any remand proceedings, without the need for any further proceedings as to those issues in this Action (D.I. 74);

WHEREAS, on January 8, 2018, the PTAB issued a Final Written Decision holding that claims 44-46 and 53 of the '221 patent are unpatentable;

WHEREAS, on October 4, 2019, in *OSI Pharmaceuticals, LLC v. Apotex Inc. et al.*, No. 18-1925, the Court of Appeals for the Federal Circuit issued an Opinion reversing the PTAB's decision that claims 44-46 and 53 of the '221 patent were unpatentable as obvious

without remand and holding that the petitioners had failed to prove that the claims were invalid (Ex. A);

WHEREAS, within five (5) days of issuance of a mandate by the Federal Circuit the January 25, 2017 Order requires the parties to jointly notify the Court in writing of the completion of the appeal and enter a joint stipulation of final judgment in this Action concerning the validity of claims 44, 46, and 53 of the '221 patent, consistent with the Federal Circuit decision, and infringement of claims 44, 46, and 53 of the '221 patent, which the parties agree will not be appealable;

WHEREAS, the mandate issued November 22, 2019;

WHEREAS, the ANDA was approved by the FDA on November 5, 2019;

NOW THEREFORE, subject to the approval of the Court, the parties hereby stipulate and agree to entry of final judgment in this action in the form below.

IT IS HEREBY ORDERED and ADJUDGED THAT:

1. Judgment is entered in favor of Plaintiffs OSI Pharmaceuticals, LLC and Genentech, Inc. and against Defendants Apotex Inc. and Apotex Corp.

The Court further finds and orders as follows:

2. The Apotex ANDA and the Apotex ANDA Product described therein infringe claims 44, 46, and 53 of the '221 patent;

3. The Apotex ANDA and the Apotex ANDA Product do not infringe claims 1-43, 45, 47-52, and 54-79 of the '221 patent;

4. Claims 44, 46 and 53 of the '221 patent are not invalid and not unenforceable;

5. Pursuant to 21 U.S.C. § 314.94(a)(12)(viii), Defendants shall notify the FDA of this Order and submit an amendment to change its Paragraph IV certification for the '221 patent to a Paragraph III certification for the '221 patent;

6. Pursuant to 35 U.S.C. § 27l(e)(4)(A), the effective date of any FDA approval of the Apotex ANDA shall not be earlier than May 9, 2021;

7. Pursuant to 35 U.S.C. § 27l(e)(4)(B) and unless permitted by license, Defendants, their officers, directors, agents, attorneys, and employees, and those in privity or active concert and participation with them who receive actual notice of this judgment by personal service or otherwise, shall be and hereby are enjoined from engaging in the commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States of the Apotex ANDA Product prior to November 9, 2020;

8. The parties expressly waive any right to appeal this Stipulated Final Judgment; and

9. The parties shall bear their own costs, expenses, and attorneys' fees.

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December 2, 2019

SO ORDERED this 4th day of December 2019.

The Honorable Colm F. Connolly
United States District Court Judge

EXHIBIT A

United States Court of Appeals for the Federal Circuit

OSI PHARMACEUTICALS, LLC,
Appellant

v.

APOTEX INC., APOTEX CORP., APOTEX PHARMACEUTICALS HOLDINGS INC., APOTEX HOLDINGS INC.,
Appellees

UNITED STATES,
Intervenor

2018-1925

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. IPR2016-01284.

Decided: October 4, 2019

THOMAS SAUNDERS, Wilmer Cutler Pickering Hale and Dorr LLP, Washington, DC, argued for appellant. Also represented by AMY K. WIGMORE, AMANDA L. MAJOR; EMILY R. WHELAN, KEVIN M. YURKERWICH, Boston, MA.

WILLIAM BLAKE COBLENTZ, Cozen O'Connor, Washington, DC, argued for appellees. Also represented by BARRY

P. GOLOB, AARON S. LUKAS, KERRY BRENDAN MCTIGUE.

DENNIS FAN, Appellate Staff, Civil Division, United States Department of Justice, Washington, DC, argued for intervenor. Also represented by KATHERINE TWOMEY ALLEN, JOSEPH H. HUNT, SCOTT R. MCINTOSH; THOMAS W. KRAUSE, JOSEPH MATAL, FARHEENA YASMEEN RASHEED, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA.

Before NEWMAN, TARANTO, and STOLL, *Circuit Judges*.

STOLL, *Circuit Judge*.

OSI Pharmaceuticals, LLC appeals the decision of the Patent Trial and Appeal Board holding claims 44–46 and 53 of U.S. Patent No. 6,900,221 unpatentable as obvious. We conclude that the Board's finding of reasonable expectation of success is not supported by substantial evidence and reverse the Board's obviousness determination.

BACKGROUND

I. Non-Small Cell Lung Cancer and the '221 Patent

Non-small cell lung cancer (NSCLC) was the leading cause of cancer deaths in 2000, claiming more than 1 million lives. The standard for treating NSCLC at the time was chemotherapy, which ameliorated some lung cancer-related symptoms, but was limited in use due to toxicity. Chemotherapy nonspecifically kills normal proliferating cells in addition to cancerous cells, and can result in the patient experiencing side effects such as nausea, vomiting, hair loss, and neuropathy.

By the late 1990s, there was a recognized need for a new therapy that would be both effective and well tolerated. In response, investigators pursued targeted therapies as alternatives to chemotherapy. One avenue of research involved investigating agents that inhibit the

epidermal growth factor receptor (EGFR). Activation of the EGFR triggers a cascade of events leading to cell reproduction, and it was hypothesized that inhibiting the EGFR would be beneficial in treating tumor cells. EGFR inhibitors were investigated as potential agents for treating NSCLC, but many of these compounds failed in clinical trials.

Cancer treatment is highly unpredictable. Even though the EGFR was identified in some cancers as a drug target, the *in vitro* (i.e., in a test tube) effectiveness of a drug in inhibiting the EGFR turned out to be a poor proxy for how effective that drug actually was in treating cancer *in vivo* (i.e., in the body). Numerous EGFR inhibitors that showed promising *in vitro* activity failed for a variety of reasons. These included poor pharmacokinetics due to poor absorption or rapid metabolism (or both), undesirable drug-drug interactions, drug toxicity due to drug binding onto healthy cells, drug toxicity due to binding onto other receptors, and metabolite toxicity. Some drug candidates were limited by one or more of these shortcomings, further underscoring the unpredictable nature of cancer treatment.

A drug compound must pass three phases of human clinical trials in order to obtain FDA approval. A threshold step is to gain the FDA's permission to test the compound in humans in the first place. After a drug developer has conducted preclinical studies, i.e., tested the compound *in vitro* (in a test tube; outside of a living organism) and in animals, it submits an Investigational New Drug (IND) application to the FDA. An IND submission includes an investigator's brochure, which discloses information such as animal safety and preclinical efficacy data, clinical trial proposals, and toxicology data. If the FDA approves the IND, then Phase I studies can commence. Phase I studies involve administering the compound to a small group of healthy volunteers or advanced cancer patients with a variety of tumor types. Phase I studies are conducted

primarily to evaluate safety, to determine a safe dosing range, and to identify any side effects.

Clinical trials do not focus on efficacy until Phase II, which typically involves administering the compound to a specific patient population. The goals of a Phase II study include evaluating efficacy in specific patient populations, determining dose tolerance and optimal dosage, and identifying possible adverse effects and safety risks. Phase III studies are larger scale and are undertaken to evaluate clinical efficacy and safety in an expanded patient population. After completing Phase III studies, a developer submits a New Drug Application to the FDA for approval.

A great majority of therapies for NSCLC failed in clinical trials. "In non-small-cell lung cancer alone, between 1990 and 2005, a total of 1,631 new drugs were studied in phase II. Only seven of these new agents gained FDA approval." Govindan at 1;[1] J.A. 4131. One of the compounds that ultimately gained FDA approval was N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, also known as erlotinib. OSI markets erlotinib under the name Tarceva®.

After years of study, the inventors of erlotinib discovered that it was an effective targeted therapy for NSCLC. They claimed their invention in the '221 patent. OSI's '221 patent issued on May 31, 2005 and claims priority to three provisional applications filed on November 11, 1999, March 30, 2000, and May 23, 2000. The '221 patent is listed in the Orange Book for Tarceva®. Claims 44–46 and 53 are at issue in this appeal and are reproduced below:

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[1] Ramaswamy Govindan, MD, *Phase III Failure Rates in Oncology Drugs Unacceptable*, 16 ONCOLOGY NEWS INT'L at 1 (Aug. 2007), https://www.cancernetwork.com/articles/phase-iii-failure-rates-oncology-drugs-unacceptable.

> 44. A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (H[P]V), Barrett's esophagus (pre-malignant syndrome), or neoplastic cutaneous diseases in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, or pharmaceutically acceptable salts thereof in anhydrous or hydrate forms, and a carrier.
>
> 45. The method of claim 44, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.
>
> 46. The method of claim 44, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).
>
> 53. The method of claim 44 for the treatment of non-small cell lung cancer (NSCLC).

'221 patent col. 35 ll. 26–42, 64–65. It is not disputed that the date of invention for the asserted claims is March 30, 2000.

II. Asserted Prior Art

The Board determined that '221 patent claims 44–46 and 53 would have been obvious over Schnur[2] in view of Gibbs[3] or OSI's 10-K.[4] We discuss each reference in turn.

A. Schnur

Schnur relates to a class of "4-(substituted phenylamino)quinazoline derivatives which are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals." Schnur col. 1 ll. 9–11. Schnur specifically discloses 105 different compounds recited as examples. *Id.* at col. 17 l. 5–col. 36 l. 61. Erlotinib is listed as a preferred compound, and a method for synthesizing erlotinib is described. *Id.* at col. 4 ll. 8–9, col. 22 ll. 30–49. Schnur states that these compounds are "potent inhibitors of the erbB family of oncogenic and protooncogenic protein tyrosine kinases such as epidermal growth factor receptor (EGFR), erbB2, HER3, or HER4 and thus are all adapted to therapeutic use as antiproliferative agents (e.g., anticancer) in mammals, particularly humans." *Id.* at col. 14 ll. 1–6. It also discloses that the compounds in this class are therapeutics "for the treatment of a variety of human tumors (renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, *lung*, vulval, thyroid, hepatic carcinomas, sarcomas, glioblastomas, various head and neck tumors), and other hyperplastic conditions such as benign hyperplasia of the skin (e.g., psoriasis) or prostate." *Id.* at col. 14 ll. 7–14 (emphasis added). While Schnur states that lung cancer is one of the many conditions that

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[2] U.S. Patent No. 5,747,498.

[3] Jackson B. Gibbs, *Anticancer Drug Targets: Growth Factors and Growth Factor Signaling*, 105 J. CLINICAL INVESTIGATION 9, 9–13 (2000).

[4] OSI Pharmaceuticals, Inc., Annual Report (Form 10-K) (Sept. 30, 1998).

could be treated by this class of compounds, it does not discuss NSCLC.

B. Gibbs

Gibbs is a review article authored by Dr. Jackson B. Gibbs. Gibbs discusses various signaling mechanisms in the cell and how they are associated with tumor malignancy. The article reviews and discusses the data of over thirty published research studies, including one discussing erlotinib, which Gibbs refers to as CP-358,774. Gibbs states that the EGFR is a drug development target and notes:

> ZD-1839 and [erlotinib], competitive inhibitors of ATP binding to the [EGFR]'s active site, are currently in clinical trials (12, 13). . . . However, these compounds appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, particularly in patients with non-small cell lung cancer.

J.A. 1406. Gibbs's reference 12 refers to Woodburn,[5] a study investigating the antitumor effects of the ZD-1839 compound—a different compound than erlotinib—on several solid human cancers including NSCLC. Woodburn does not discuss erlotinib at all. Reference 13 refers to Moyer,[6] which discloses how erlotinib inhibits EGFR in mouse liver tumors and in human HN5 tumors. J.A. 1524. Moyer does not discuss NSCLC at all, let alone suggest that

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[5] J.R. Woodburn et al., *ZD1839, An Epidermal Growth Factor Tyrosine Kinase Inhibitor Selected for Clinical Development*, 38 PROC. AM. ASS'N FOR CANCER RES. ANN. MEETING 633, 633 (1997).

[6] J.D. Moyer, et al., *Induction of Apoptosis and Cell Cycle Arrest by CP-358,774, an Inhibitor of Epidermal Growth Factor Receptor Tyrosine Kinase*, 57 CANCER RES. 4838, 4838–48 (1997).

erlotinib could treat NSCLC. There is no data regarding the use of erlotinib to treat NSCLC in Gibbs or in any of the references cited in Gibbs. Dr. Gibbs, the author, confirmed this in a declaration submitted to the Board:

> Based on references 12 and 13, the abstracts from the 1999 ASCO and AACR Conferences, and my own personal recollection, my research at the time of my article did not identify any information suggesting that [erlotinib] exhibited anti-tumor activity in NSCLC. I was (and still am) not aware of any published abstracts or articles describing the clinical or preclinical response of a NSCLC tumor to [erlotinib] that were available as of the time my article was published, and I reviewed no such abstracts or articles in drafting my article.

J.A. 4803.

C. OSI's 10-K

The SEC requires domestic public companies to submit a Form 10-K annually and has stated that the "Form 10-K provides a comprehensive overview of the company's business and financial condition and includes audited financial statements." J.A. 5313. OSI's 10-K, filed for the fiscal year that ended on September 30, 1998, disclosed varied business information, including information on OSI's finances, product development, research, competition, and manufacturing. *See* J.A. 1411–88. In the section titled Product Development and Research Programs, OSI's 10-K stated:

> [Erlotinib], which targets a variety of cancers including ovarian, pancreatic, non-small cell lung and head and neck, achieved a significant milestone with the completion of Phase I safety trials and the initiation of Phase II clinical trials in the United States in cancer patients. [Erlotinib] is a potent, selective and orally active inhibitor of the

> epidermal growth factor receptor, a key oncogene in these cancers.

J.A. 1415.

It is undisputed that OSI's 10-K discloses no data regarding erlotinib's effect on NSCLC. *See* J.A. 4562. OSI's expert, Dr. Paul Bunn, explained that IND submissions (required for Phase I studies) include an investigator's brochure, which Dr. Bunn explained has the following information:

> So you have to have toxicology studies so you know what a lethal dose is, you have to have pharmacokinetic data so you know how the drug behaves in an animal, and you have to have a clinical trial, proposed clinical trial. The clinical trial has to be approved by an IRB before an IND would be activated. And you have to have *all the preclinical efficacy data, as well as the animal safety data.*

J.A. 1991–92 (emphasis added). He further testified that the investigator's brochure "would list the indications that you are going to study and the clinical trial that has to accompany, would specify what patients are being included." J.A. 1993.

III. Procedural History

The Board instituted IPR on grounds that claims 44–46 and 53 of the '221 patent would have been obvious over Schnur in view of Gibbs or OSI's 10-K. *Apotex Inc. v. OSI Pharm. LLC*, No. IPR2016-01284, 2018 WL 335096, at *2 (P.T.A.B. Jan. 8, 2018) ("*Decision*"). The parties agreed that the definition of "treating" provided in the specification is the proper construction of the term. The '221 patent defines "treating" as "reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition." '221 patent col. 14 ll. 9–13. The Board clarified that the term "therapeutically effective

amount" in claim 44 means "an amount sufficient to treat the mammal" as defined by the patent specification. *Decision*, 2018 WL 335096, at *3.

The Board reviewed the prior art references and found that a person of ordinary skill "would have combined Gibbs or OSI 10-K with Schnur and had a reasonable expectation of success of achieving the invention of challenged claims 44 and 53." *Id.* at *11. It found that Schnur discloses all of the limitations of claims 44 and 53 except for the treatment of NSCLC. *Id.*

The Board found that the disclosures in OSI's 10-K that erlotinib targeted a variety of cancers including NSCLC, and that erlotinib had entered Phase II clinical trials, would have provided a person of ordinary skill with a reasonable expectation of success in light of Schnur's teachings. *Id.* at *15. Although nothing in the record indicated that any preclinical data related to NSCLC existed, the Board concluded that an ordinary artisan would understand from the commencement of Phase I studies that "preclinical animal efficacy data" had been submitted to the FDA. *Id.* at *12.

It found similarly with regard to Gibbs, focusing on Gibbs's disclosure that "[ZD-1839 and erlotinib] appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index particularly in patients with non-small cell lung cancer." *Id.* at *17. Although unsupported by any data or the cited Moyer or Woodburn references, the Board credited and relied on this statement. It also discounted the testimony of Dr. Gibbs—the author of the Gibbs article—who declared that his article was not based on any clinical or preclinical data showing the effect of erlotinib on NSCLC. *Id.* at *18. The Board ultimately concluded that claims 44 and 53 "are rendered obvious by the combination of Schnur and OSI's 10-K, as well as the combination of Schnur and Gibbs." *Id.* at *22. Because OSI did not separately argue claims 45–46, the Board

concluded that those claims were also unpatentable for the same reasons. *Id.*

OSI appeals, and we have jurisdiction under 28 U.S.C. § 1295(a)(4)(A).

DISCUSSION

We review the Board's legal conclusions de novo and its fact findings for substantial evidence. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1366 (Fed. Cir. 2016). Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. N.L.R.B.*, 305 U.S. 197, 229 (1938). The substantial evidence standard asks "whether a reasonable fact finder could have arrived at the agency's decision," and "involves examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000). The Supreme Court "has stressed the importance of not simply rubber-stamping agency factfinding. . . . The [Administrative Procedure Act] requires meaningful review; and its enactment meant stricter judicial review of agency factfinding than Congress believed some courts had previously conducted." *Dickinson v. Zurko*, 527 U.S. 150, 162 (1999). "Mere speculation" is not substantial evidence. *See Intellectual Ventures I LLC v. Motorola Mobility LLC*, 870 F.3d 1320, 1331 (Fed. Cir. 2017).

In the district court litigation setting, where to avoid summary judgment against the plaintiff "there must be evidence on which [a] jury could reasonably find for the plaintiff," the Supreme Court has explained that the assessment of what the jury could reasonably find "necessarily implicates the substantive evidentiary standard of proof that would apply at the trial on the merits," and "must be guided by the substantive evidentiary standards that apply to the case." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 252–56 (1986) (discussing standard for directed verdict).

Accordingly, substantial evidence is not a fixed quantum of evidence, and may only be determined with respect to the standard of proof. *See Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1363 (Fed. Cir. 2004) ("[I]n reviewing whether the evidence supports a finding of fact . . . the decision might be affirmed if the standard of proof below were 'weight of evidence' and might be reversed on the same record if the standard of proof were 'clear and convincing' evidence." (alteration in original) (quoting *SSIH Equip. S.A. v. U.S. Int'l Trade Comm'n*, 718 F.2d 365, 383 (Fed. Cir. 1983) (Nies, J., additional comments)). The same point logically applies to review of the Board's finding. *See In re Hotels.com, L.P.*, 573 F.3d 1300, 1302 (Fed. Cir. 2009) (substantial evidence inquiry in review of Patent Office trademark decision must take account of standard of proof). In the IPR here, the burden was on Apotex to establish invalidity by a preponderance of the evidence. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144 (2016).

OSI challenges the Board's obviousness determination, arguing that the Board's finding of a reasonable expectation of success is not supported by substantial evidence. It also raises a challenge to the constitutionality of IPR. We address each issue in turn.

I

"Obviousness is a question of law based on underlying findings of fact." *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009). "An obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the teachings in the prior art and would have had a reasonable expectation of success in doing so." *Regents of Univ. of Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291 (Fed. Cir. 2018). "Whether a person of ordinary skill in the art would have been motivated to modify or combine teachings in the prior art, and whether he would have had a reasonable expectation of

success, are questions of fact." *Id.* (quoting *In re Stepan Co.*, 868 F.3d 1342, 1345–46 (Fed. Cir. 2017)).

The Board found that the asserted combinations of Schnur with Gibbs and Schnur with OSI's 10-K each would have provided a person of ordinary skill with a reasonable expectation of success in using erlotinib to treat NSCLC in a mammal. *Decision*, 2018 WL 335096, at *22. We conclude that these findings are not supported by substantial evidence. As an initial matter, in reaching its conclusion, the Board misinterpreted the asserted references to teach more than substantial evidence supports. When the references are properly read, the Board's finding that the asserted references provide a reasonable expectation of success also is not supported by substantial evidence. To be clear, the claims require only treatment of a *mammal* with erlotinib—efficacy in humans is not required. But the asserted references do not disclose *any* data or other information about erlotinib's efficacy in treating NSCLC. The record does not contain any clinical (human) data or preclinical (animal) data. It does not even include *in vitro* (test tube) data regarding erlotinib's effect on NSCLC. At the same time, it is undisputed that NSCLC treatment was highly unpredictable with an over 99.5% rate of failure for drugs entering Phase II clinical studies. On this record, we are not persuaded that a reasonable factfinder could conclude that a person of ordinary skill would have reasonably expected success based on the combination of Schnur and Gibbs or Schnur and OSI's 10-K.

A

We begin by addressing the Board's erroneous reading of Gibbs. The Board found that there is a "clear inference" in Gibbs that "erlotinib has anti-cancer activity against non-small cell lung cancer." *Decision*, 2018 WL 335096, at *17. This finding is not supported by substantial evidence.

> Gibbs discloses the following:
>
> ZD-1839 and [erlotinib], competitive inhibitors of ATP binding to the receptor's active site, are currently in *clinical trials (12, 13)*. Their mechanism of action has led to some concern about safety, given the variety and physiological significance of protein kinases and other enzymes that bind ATP. However, *these compounds* appear to have good anti-cancer activity in preclinical models, with an acceptable therapeutic index, *particularly in patients with non-small cell lung cancer*.

J.A. 1406 (emphases added). Gibbs is a review article that collects, reviews, and analyzes other research studies. As such, the above passage relies on references 12 and 13 to support its discussion about anti-cancer activity. And because Dr. Gibbs was not reporting on his own first-hand research, the only support for the sentence that "these compounds appear to have good anti-cancer activity . . . particularly in patients with non-small cell lung cancer" comes from references 12 and 13.

Reference 12 is Woodburn, which discloses that ZD-1839 "shows antitumor activity in a broad range of human solid tumor xenografts" including NSCLC. J.A. 4124. There is no mention of erlotinib in Woodburn. Reference 13 is Moyer, which discloses that erlotinib shows anti-cancer activity in human head and neck tumors (xenografted in mice), mouse liver tumors, and human colorectal cell-lines. *See* J.A. 1524. Moyer does not mention NSCLC at all. Apotex's expert, Dr. Giaccone, agreed: "Q. But we've agreed that Moyer does not talk about non-small cell lung cancer, correct? A. Yes." J.A. 4602.

Moyer and Woodburn are the only two references cited in Gibbs supporting the statement that ZD-1839 and erlotinib show good anti-cancer activity "in patients with non-small cell lung cancer." Reading Gibbs in the context of its cited articles reveals that this statement cannot be

referring to erlotinib. That is because only Woodburn mentions NSCLC, and Woodburn does not mention erlotinib at all. Indeed, there is no evidence that a publication discussing erlotinib's effect on NSCLC existed at the time Gibbs was published. Dr. Gibbs himself confirmed in a declaration before the Board that he was not aware of any such publication and that he reviewed no such publication when drafting his article. *See* J.A. 4803.

On this record, the Board's finding that there is a "clear inference" in Gibbs that "erlotinib has anti-cancer activity against non-small cell lung cancer" is thus not supported by substantial evidence. *Decision*, 2018 WL 335096, at *17. The substantial evidence standard "involves examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *In re Gartside*, 203 F.3d at 1312. The Board erred by not properly considering that none of the cited articles supported its reading of Gibbs, as well as Dr. Gibbs's testimony to that effect.

B

We turn next to the Board's findings on reasonable expectation of success. The Board found that the asserted combinations of Schnur with Gibbs and Schnur with OSI's 10-K each would have provided a person of ordinary skill with a reasonable expectation of success in using erlotinib to treat NSCLC in a mammal. *Decision*, 2018 WL 335096, at *22. We conclude that, properly read, these combinations do not provide substantial evidence supporting the Board's findings of reasonable expectation of success.

Turning first to Schnur in view of Gibbs, the asserted references do not disclose any information about erlotinib's efficacy in treating NSCLC in a mammal. Schnur broadly discloses at least 105 compounds for the treatment of twelve different types of cancer. There is no dispute that Schnur fails to disclose any *in vitro* or *in vivo* efficacy data for erlotinib or otherwise suggest the use of erlotinib to

treat NSCLC. *See* J.A. 5389. Schnur's deficiencies are not cured by Gibbs. Properly read in context, Gibbs discloses only that erlotinib inhibits the EGFR and has good anti-cancer activity in some cancers, *not* including NSCLC. These references thus contain no data or other promising information regarding erlotinib's efficacy in treating NSCLC.

The lack of erlotinib-NSCLC efficacy data or other indication of success here is significant because of the highly unpredictable nature of treating NSCLC, which is illustrated by the over 99.5% failure rate of drugs entering Phase II. *See* J.A. 4131. Indeed, this failure rate includes only drug candidates that were promising enough to make it to Phase II trials, and does not even take into account all of the drug candidates that failed in the preclinical stage and in Phase I studies. Further, it is undisputed that a drug's success in treating one type of cancer does not necessarily translate to success in treating a different type of cancer, which underscores the unpredictability in cancer treatment generally. Apotex's own expert Dr. Giaccone admitted as much:

> Q: And do you agree that some drugs may work for certain tumor types, but not others?
>
> . . .
>
> A: Again, in general terms, drugs can work on some specific tumor types and not others.
>
> Q: So just because a compound has been shown to treat one type of cancer does not mean it will succeed in treating another type of cancer, correct?
>
> A: That's correct.

J.A. 4532. And while EGFR was a drug development target for cancer, there is no finding by the Board and no assertion by Apotex that EGFR inhibition alone is indicative of treatment success. Thus, there is not only a complete

absence of data regarding the effect of erlotinib on NSCLC, but also a complete absence of an indicator or mechanism on which a person of ordinary skill could rely to reasonably expect success.

The combination of Schnur and OSI's 10-K similarly fails to provide a reasonable expectation of success. In finding that Apotex had met its burden of establishing a reasonable expectation of success, the Board emphasized the 10-K's statement that erlotinib had completed Phase I clinical trials. It also relied on Dr. Bunn's testimony that a drug's IND submission contains preclinical efficacy and animal safety data. The Board then found that "Dr. Bunn's testimony is evidence that the ordinary artisan would understand that the filing of an IND and investigative brochures with the FDA, which need to be submitted to the FDA before starting Phase I trials, require preclinical animal efficacy data." *Decision*, 2018 WL 335096, at *12. It also cited Dr. Giaccone's testimony that the claim limitation "therapeutically effective amount" can be met by a showing of a therapeutic benefit in an animal, i.e., in a preclinical study. *Id.* at *13. From this, the Board found that a person of ordinary skill would have reasonably expected success in combining Schnur with OSI's 10-K. *Id.* at *15. Notably absent from this combination, however, is any data or other information regarding erlotinib's effect on NSCLC. There is nothing in OSI's 10-K suggesting the existence of erlotinib preclinical efficacy data that is specific to NSCLC. Even if a skilled artisan could presume that some preclinical data exists, there is no basis for assuming that the data pertains to NSCLC as opposed to other cancers. And just because the EGFR is targeted by a drug does not necessarily mean that the drug will treat NSCLC. *See* J.A. 4695 (Dr. Bunn testifying that several EGFR inhibitors that showed promising *in vitro* activity failed later in the drug development process).

Moreover, between 1990 and 2005, a period that includes the time of the invention, there were 1,630 other

new drug compounds that, like erlotinib, targeted NSCLC and were studied in Phase II trials. The failure rate for these compounds was 99.5%. The Board did not properly consider OSI's 10-K statement in light of the 99.5% failure rate of the other 1,630 drugs entering Phase II trials for the treatment of NSCLC. Given this high failure rate, a fact finder could not reasonably find that the 10-K statement combined with Schnur would have been sufficient to create a reasonable expectation of success. These references provide no more than hope—and hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art such as this. Indeed, given a 99.5% failure rate and no efficacy data or any other reliable indicator of success, the only reasonable expectation at the time of the invention was failure, not success. It is only with the benefit of hindsight that a person of skill in the art would have had a reasonable expectation of success in view of the asserted references.

To be clear, we do not hold today that efficacy data is always required for a reasonable expectation of success. Nor are we requiring "absolute predictability of success." *See* Appellee's Br. 39. We conclude only that, on these particular facts, a reasonable fact finder could not find a reasonable expectation of success. The Board's finding is thus not supported by substantial evidence, and accordingly we reverse its obviousness determination.

II

OSI also challenged the constitutionality of the Board's IPR decision in its opening appellate brief.[7] *See*

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[7] We exercise our discretion and reach OSI's argument rather than finding that OSI waived this issue by failing to present it to the Board. *See In re DBC*, 545 F.3d 1373, 1379–80 (Fed. Cir. 2008) (noting "discretion to reach

Appellant's Br. 49–50. Specifically, OSI questioned the constitutionality of retroactively applying IPRs to pre-AIA patents like the '221 patent and noted that the Supreme Court's decision in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, 138 S. Ct. 1365 (2018), did not reach this issue. *See* Appellant's Br. 49–50. After OSI submitted its opening appellate brief, the government intervened to defend the Board. *See* Motion of United States for Leave to Intervene, OSI Pharm., LLC v. Apotex Inc., No. 18-1925 (Fed. Cir. Nov. 5, 2018), ECF No. 29.

Following oral argument in this case, we issued multiple decisions holding that the application of IPR to pre-AIA patents does not violate the Constitution. *See e.g., Celgene Corp. v. Peter*, 931 F.3d 1342, 1362 (Fed. Cir. 2019); *Arthrex, Inc. v. Smith & Nephew, Inc.*, No. 2018-1584, 2019 WL 3938271, at *7 (Fed. Cir. Aug. 21, 2019). In *Celgene*, 931 F.3d at 1359, we explained that pre-AIA patents were issued subject to both district court and Patent Office validity proceedings. Though IPR differs from district court and pre-AIA Patent Office proceedings, we held that those differences were not sufficiently substantive or significant such that a "constitutional issue" is created when IPR is applied to pre-AIA patents. *Id.* at 1362.

The government cited our decisions as supplemental authority under Fed. R. App. P. 28(j), and in response, OSI conceded that our decisions "foreclose [OSI's] constitutional challenge at the panel stage." Response of Appellant OSI to Supplemental Authority at 1, OSI Pharm., LLC v. Apotex Inc., No. 18-1925 (Fed. Cir. Aug. 22, 2019), ECF No. 60. Accordingly, we hold that the Board's decision does not create a constitutional issue.

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issues raised for the first time on appeal" but holding party waived constitutional challenge based on Appointments Clause by failing to raise it before the Board).

CONCLUSION

We have considered Apotex's remaining arguments and find them unpersuasive. The Board's finding of a reasonable expectation of success is not supported by substantial evidence. Accordingly, we reverse the Board's determination of obviousness.

REVERSED